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# MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network

Giovanni Battista Migliori[a,*], Simon Tiberi[b,c], Alimuddin Zumla[d], Eskild Petersen[e,f,g], Jeremiah Muhwa Chakaya[h,i], Christian Wejse[j], Marcela Muñoz Torrico[k], Raquel Duarte[l], Jan Willem Alffenaar[m,n,o], H. Simon Schaaf[p], Ben J. Marais[q,r], Daniela Maria Cirillo[s], Riccardo Alagna[s], Adrian Rendon[t], Emanuele Pontali[u], Alberto Piubello[h,v], José Figueroa[w], Gabriella Ferlazzo[x], Alberto García-Basteiro[y,z], Rosella Centis[a], Dina Visca[A,B], Lia D'Ambrosio[C], Giovanni Sotgiu[D], the members of the Global Tuberculosis Network[1]

[a] Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS, Via Roncaccio 16, Tradate, Varese, 21049, Italy
[b] Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom
[c] Division of Infection, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom
[d] Division of Infection and Immunity, University College London and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, United Kingdom
[e] Directorate General for Disease Surveillance and Control, Ministry of Health, Muscat, Oman
[f] Institute for Clinical Medicine, Faculty of Health Science, University of Aarhus, Denmark
[g] ESCMID Emerging Infections Task Force, Basel, Switzerland
[h] The International Union Against Tuberculosis and Lung Disease, Paris, France
[i] Department of Medicine, Therapeutics, Dermatology and Psychiatry, Kenyatta University, Nairobi, Kenya
[j] Department of Infectious Disease, Aarhus University Hospital and School of Public Health, Faculty of Health Sciences, University of Aarhus, Denmark
[k] Clínica de Tuberculosis, Instituto Nacional de Enfermedades Respiratorias, Ciudad de México, Mexico
[l] National Reference Centre for MDR-TB, Hospital Centre Vila Nova de Gaia, Department of Pneumology, Public Health Science and Medical Education Department, Faculty of Medicine, University of Porto, Porto, Portugal
[m] Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia
[n] Westmead Hospital, Sydney, Australia
[o] Dept. Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands
[p] Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa
[q] The University of Sydney Faculty of Medicine and Health, Sydney, New South Wales, Australia
[r] The University of Sydney Marie Bashir Institute for Infectious Diseases and Biosecurity, Sydney, New South Wales, Australia
[s] Emerging Pathogens Unit, TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Milan, Italy
[t] Centro de Investigación, Prevención y Tratamiento de Infecciones Respiratorias CIPTIR, University Hospital of Monterrey UANL (Universidad Autonoma de Nuevo Leon), Monterrey, Mexico
[u] Department of Infectious Diseases, Galliera Hospital, Genova, Italy
[v] Tuberculosis Division, Damien Foundation, Niamey, Niger
[w] National Health Service (NHS) England, London, United Kingdom
[x] Southern Africa Medical Unit, Médecins Sans Frontières, Cape Town, South Africa
[y] Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique
[z] ISGlobal, Barcelona Centre for International Health Research, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain
[A] Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy
[B] Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese, Italy
[C] Public Health Consulting Group, Lugano, Switzerland
[D] Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy

* Corresponding author.
*E-mail addresses:* giovannibattista.migliori@icsmaugeri.it (G.B. Migliori), simon.tiberi@nhs.net (S. Tiberi), a.i.zumla@gmail.com (A. Zumla), eskild.petersen@gmail.com (E. Petersen), chakaya.jm@gmail.com (J.M. Chakaya), wejse@dadlnet.dk (C. Wejse), dra_munoz@hotmail.com (M. Muñoz Torrico), raquelafduarte@gmail.com (R. Duarte), j.w.c.alffenaar@umcg.nl (J.W. Alffenaar), hss@sun.ac.za (H. S. Schaaf), ben.marais@health.nsw.gov.au (B.J. Marais), cirillo.daniela@hsr.it (D.M. Cirillo), alagna.riccardo@hsr.it ( adrianrendon@hotmail.com (A. Rendon), pontals@yahoo.com (E. Pontali), albertopiubello@yahoo.it (A. Piubello), josefigueroa@doctors.org.uk (J. Figueroa), Gabriella.FERLAZZO@joburg.msf.org (G. Ferlazzo), alberto.garcia-basteiro@manhica.net (A. García-Basteiro), rosella.centis@icsmaugeri.it (R. Centis), dina.visca@icsmaugeri.it (D. Visca), liadambrosio59@gmail.com (L. D'Ambrosio), gsotgiu@uniss.it (G. Sotgiu).
[1] The members of the Global Tuberculosis Network are listed in Appendix A.

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ABSTRACT

The continuous flow of new research articles on MDR-TB diagnosis, treatment, prevention and rehabilitation requires frequent update of existing guidelines. This review is aimed at providing clinicians and public health staff with an updated and easy-to-consult document arising from consensus of Global Tuberculosis Network (GTN) experts.

The core published documents and guidelines have been reviewed, including the recently published MDR-TB WHO rapid advice and ATS/CDC/ERS/IDSA guidelines.

After a rapid review of epidemiology and risk factors, the clinical priorities on MDR-TB diagnosis (including whole genome sequencing and drug-susceptibility testing interpretations) and treatment (treatment design and management, TB in children) are discussed. Furthermore, the review comprehensively describes the latest information on contact tracing and LTBI management in MDR-TB contacts, while providing guidance on post-treatment functional evaluation and rehabilitation of TB sequelae, infection control and other public health priorities.



## Introduction

Multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) still represent a challenge for clinicians and staff operating in national TB programmes (Akkerman et al., 2019; Borisov et al., 2017, 2019; Lange et al., 2019, 2014; Nahid et al., 2019; World Health Organization, 2019a, 2019b; Migliori and Global Tuberculosis Network (GTN), 2019).

Although reviews on MDR-TB diagnosis, treatment, prevention and rehabilitation have been recently published (Lange et al., 2014; Lange et al., 2019), they are warranted by the rapid turnover of recommendations and guidelines from the World Health Organization (WHO) (World Health Organization, 2019b) and scientific societies (Nahid et al., 2019).

The aim of this review is to provide clinicians and public health staff an updated and easy-to-consult document arising from consensus of Global Tuberculosis Network (GTN) experts.

## Methods

A non-systematic search of the literature was performed using the key words 'MDR-TB'/'XDR-TB' to identify a minimum set of core references from electronic databases (MEDLINE, PUBMED), existing guidelines and grey literature. A writing committee composed of internationally known experts was created, complemented by experts from the members of the GTN (Treatment and Consilium committees and other Committees' chairs, see acknowledgements) and consensus on the content was reached after multiple rounds of revision (Akkerman et al., 2019; Borisov et al., 2019). WHO definitions were used (e.g. MDR-/XDR-TB, treatment outcomes) (Migliori and Global Tuberculosis Network (GTN), 2019; World Health Organization, 2019a, 2019b). As this review is not aimed at duplicating WHO and other existing guidelines, the GRADE methodology (Nahid et al., 2019; World Health Organization, 2019b) was not used, and no formal recommendations are provided.

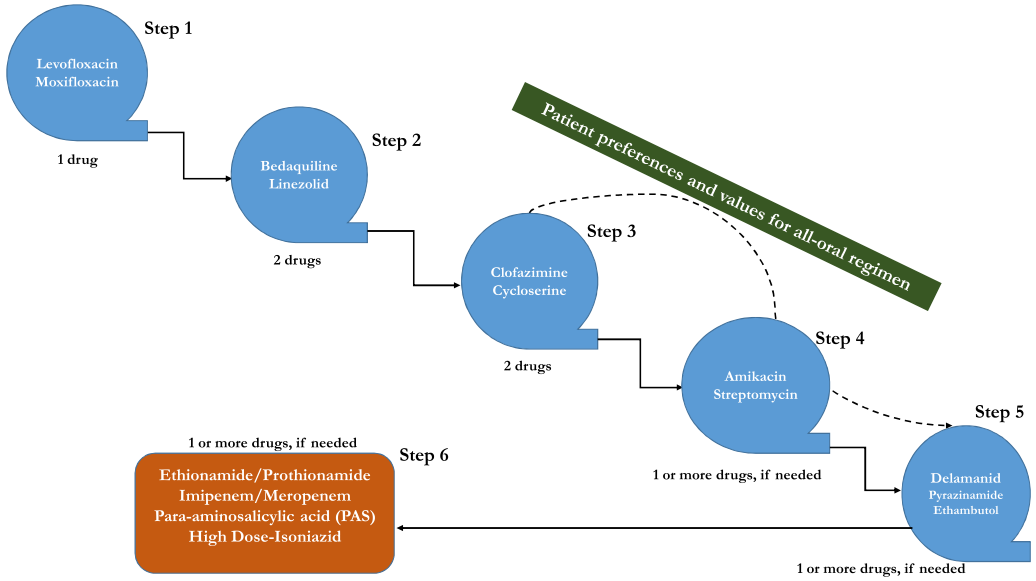


**Figure 1.** How to design the regimen for multidrug-resistant tuberculosis.
In the text and figure we focus mainly on the ATS/CDC/ERS/IDSA guideline, as - although largely consistent with the 2019 WHO ones - they provide additional clinical elements with main focus on low-TB incidence countries. Additional minor differences include less focus on injectables and the WHO shorter regimen, more focus on tailoring the regimen to drug-resistances identified, a larger number of drugs and a slightly different prioritization of the drugs.
The 2019 WHO MDR-TB guidelines recommend that all 3 Group A drugs (bedaquiline, linezolid, levofloxacin/moxifloxacin) and 1 Group B drug (clofazimine, cycloserine/terizidone) are prescribed (4 versus 5 drugs recommended by ATS/CDC/ERS/IDSA guidelines). If only 1 or 2 Group A drugs are prescribed, both Group B drugs should be prescribed. If needed, Group C drugs (ethambutol, delamanid, pyrazinamide, imipenem, meropenem, amikacin/streptomycin, para-aminosalycilic acid, ethionamide/prothionamide) should be administered.

In this document we revised the updated available information on diagnosis, treatment and prevention of MDR-TB. The timing of publication allowed the authors to capture the content of the WHO rapid advice on MDR-TB (World Health Organization, 2019e) but not of the new WHO MDR-TB guidelines (not yet released, publication expected in early 2020). Therefore, the main focus was on the ATS/CDC/ERS/IDSA guidelines (Nahid et al., 2019). The main differences between the existing WHO guidelines and the above-mentioned ones are summarized in the legend of Figure 1.

## Epidemiology and risk factors

Elimination of TB by 2035 will only be possible if countries address the emergence of drug-resistant (DR) strains of *Mycobacterium tuberculosis* effectively. According to the WHO 2018 report, not all DR-TB cases are diagnosed (only 51% of people with bacteriologically confirmed TB were tested for rifampicin resistance (RR) in 2018), and not all DR-TB cases were treated (only one in three of the approximately half a million people who developed MDR/RR-TB in 2018 were treated). DR-TB continues to be an important public health priority (World Health Organization, 2019d), and an estimated 19 million people are latently infected with MDR-TB (Knight et al., 2019).

Prevention of DR-TB remains a key priority and cannot be achieved by early diagnosis and appropriate treatment alone but also requires preventive therapy and effective vaccination. Moreover, the main risk factors for TB should be programmatically addressed: these include poverty, overcrowding, HIV co-infection, diabetes, alcoholism, smoking, immunosuppressive and other drugs.

## Diagnosis of MDR-TB

The End TB Strategy (World Health Organization, 2019d) calls for the early diagnosis and treatment of all persons with any form of drug-susceptible or DR-TB.

Successful diagnosis and treatment of MDR-/XDR-TB rely on universal drug-susceptibility testing (DST) (Cabibbe et al., 2017; Miotto et al., 2017; World Health Organization, 2019d). Increasing access to early and accurate diagnosis using a WHO-recommended rapid diagnostic test (WRD) (Table 1) is one of the main components of the TB laboratory-strengthening efforts in the End TB Strategy. In the recent years, the advent of rapid molecular techniques, based on nucleic amplification tests (NAATs) and sequencing have represented an important breakthrough in TB diagnostics.

## WHO approved High-throughput centralized MDR-TB tests

Four PCR-based platforms, suitable for high laboratory throughput, have been approved by a WHO technical group (World Health Organization, 2019c): (a) the RealTi*m*e MTB (Abbott, Chicago, IL, United States of America [USA]); (b) the Roche Cobas MTB assay (Roche, Basel, Switzerland), (c) the FluoroType MTBDR assay (Hain Lifescience, Nehren, Germany) and (d) the BD Max MDR-TB assay (Becton Dickinson, New Jersey, USA). Each platform underwent a comparative analytical evaluation using a well-defined *M. tuberculosis* strain panel to test their sensitivity for detecting *M. tuberculosis* complex and their ability to detect key mutations conferring resistance to rifampicin and isoniazid. There are concerns that additional studies will be needed to verify the specificity of the new assays, since they use multicopy or novel DNA targets (or both) for the detection of TB. Therefore, a 2nd phase of testing will evaluate the clinical validity of the assays through testing of the platforms in up to 3 national reference laboratories in high TB burden settings. The results will be compared with the reference standards of culture, phenotypic DST, Xpert MTB/RIF Ultra and molecular sequencing.

## Next-Generation sequencing (NGS): a promising tool

NGS is rapidly gaining interest as an affordable all-in-one diagnostic solution that allows for individualised treatment. Unlike other TB diagnostic technologies providing partial information on drug-susceptibility limited by a set of resistance mutations, NGS gives comprehensive genetic information with a variety of applications ranging from diagnosis to surveillance of DR-TB. Current generation sequencing technology relies on DNA extraction from clinical samples or clinical isolates, library preparation made by collection of fragmented DNA with oligonucleotide adaptors, sequencing and data analysis. Despite the invaluable application of NGS, implementation of this technology has been hampered, among other causes, by high costs of equipment, need for technical training and guidance for clinical interpretation of generated data. The WHO has recently released a guide providing a comprehensive overview of workflow and equipment, principles to best interpret genetic data, experience in using NGS in population-based studies and, lastly, requirements for implementation in low- and middle-income countries. However, although promising, NGS will still need to achieve stringent regulatory approval, such as from the WHO, to facilitate its implementation into routine diagnostics (World Health Organization, 2018a).

## How to interpret DST

WHO (World Health Organization, 2018b) defines universal access to DST as rapid determination for at least rifampicin, and further DST for at least fluoroquinolones among all RR-TB patients. Culture-based phenotypic DST methods are currently the gold standard for DR-TB detection, but these methods are time-consuming, and require sophisticated and well established laboratory infrastructure, qualified staff and strict quality and infection control. In addition, for some drugs (fluoroquinolones, rifampicin) molecular tests could be more predictive than phenotypic tests. Traditionally, DST for *M. tuberculosis* has relied on the testing of a single, critical concentration (CC), which is used to differentiate resistant from susceptible isolates of *M. tuberculosis* and is specific for each anti-TB agent and test method. Laboratory DSTs to anti-TB agents serve four main purposes: (1) to guide the choice of an effective regimen; (2) to confirm that DR has emerged when a patient has failed to show a satisfactory response to treatment; (3) can be used for surveillance of emerging DR; (4) may guide management of close contacts of the DR-TB cases, including children.

Use of microtitre plates to determine minimal inhibitory concentrations (MICs) to multiple drugs at the same time is an appealing technology and could be usefully adopted to monitor increase of MIC in a population exposed to new drugs. WHO will release CC on microtitre plates in 2020.

To perform phenotypic DST, mycobacteria are often initially grown in a variety of solid or liquid culture media. Bacterial growth on solid medium can be identified visually (i.e. by identifying characteristic growth) or by automated detection of fluorescence in liquid medium. The MGIT (mycobacterial growth indicator tube) automated *M. tuberculosis* culture system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) indicates a reduction in the oxygen tension to confirm the detection of "*M. tuberculosis complex*" (MTBC) and excludes the presence of any nontuberculous mycobacteria or other bacteria prior to performing DST.

WHO recommends the use of rapid molecular DST as the initial test to detect DR prior to the initiation of appropriate therapy for all TB patients, including new and previously treated ones.

**Table 1**
New TB diagnostics development pipeline (adapted from World Health Organization, 2019d).

**NEW TB DIAGNOSTICS**

**TECHNOLOGIES ENDORSED BY WHO**

***Molecular detection of TB and drug resistance***
- Xpert MTB/RIF and Xpert Ultra as the initial diagnostic test for TB and rifampicin resistance, Cepheid, USA
- Line probe assays for the detection of *M. tuberculosis* (MTB), isoniazid and rifampicin resistance in acid-fast bacilli smear positive sputum or MTB cultures (FL-LPA), Hain Lifescience, Germany and Nipro, Japan
- TB LAMP for detection of TB, Eiken, Japan

***Nonmolecular* technologies**
- Interferon gamma release assay (IGRAs) for the diagnosis of latent TB infection (LTBI) Oxford Immunotec, UK; Qiagen, USA

***Culture*-based technologies**
- Commercial liquid culture systems and rapid speciation
- Culture-based phenotypic DST using 1% critical proportion in LJ,7H10,7H11 and MGIT media.

***Microscopy***
- Light and light-emitting diode microscopy (diagnosis and treatment monitoring)

***Biomarker (MTB antigen) based assays***
- Alere Determine TB-LAM, Alere, USA (TB detection in people seriously ill with HIV)

**ON THE MARKET (NOT SUBMITTED TO WHO FOR EVALUATION)**

***Molecular detection of TB and drug resistance***
- iCubate System, iCubate, USA
- Genechip, TB drug resistance array, Capital Bio, China
- EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China

**TECHNOLOGIES UNDER DEVELOPMENT**

***Molecular detection of TB and drug resistance***
- Gendrive MTB/RIF ID, Epistem, UK
- Xpert XDR-TB cartridge, Cepheid, USA
- TruArray MDR-TB, Akkoni, USA
- INFINITIMTB Assay, AutoGenomics, USA
- FluoroType XDR-TB assay, Hain Lifescience, Germany
- MeltPro TB assay, Zeesan Biotech, China
- QuantuMDx, POC, UK

***Tests for latent TB infection***
- Diaskin test, Generium, Russian Federation
- C-Tb test, Serum Institute of India, India

**SCHEDULED FOR WHO EVALUATION IN 2019/2020**

***Molecular detection of TB and drug resistance***
- Molecular technologies for genotypic drug resistance testing (including sequencing technologies)
- FluoroType MTBDR, Hain Lifescience, Germany
- m2000 RealTime MTB System, Abbott, USA
- BD Max MDR-TB, Becton Dickinson, USA
- Roche cobas® MTB system, Roche Diagnostics, Basel, Switzerland

***Radiology***
- Computer aided detection (CAD)

**WHO POLICY UPDATES SCHEDULED FOR 2019/2020**

***Molecular detection of TB and drug resistance***
- Xpert MTB/RIF Ultra for detection of TB and rifampicin resistance in pulmonary, extrapulmonary and paediatric samples, Cepheid, USA
- Truelab/Truenat MTB, Molbio/bigtec Diagnostics, India

***Culture-based drug susceptibility testing***
- SensititreTM MYCOTBI plate; ThermoFisher Scientific Inc., USA

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; IGRAs: interferon-gamma release assays; LTBI: latent tuberculosis infection; TB-LAM: tuberculosis lipoarabinomannan assay.

If RR is detected, rapid molecular tests for resistance to isoniazid, fluoroquinolones and amikacin should be performed promptly to inform which second-line drugs can be used for the treatment of RR-TB, MDR-TB and XDR-TB.

Genotypic DST methods such as NGS are attractive alternatives to culture-based DST methods given the rapidity and the detailed sequence information that can be generated for multiple gene regions associated with DR. However, until our knowledge of the molecular basis of resistance improves, culture-based DST for other important second-line drugs including bedaquiline, linezolid, and other agents will still need to be performed. One should consider performing culture-based DST for fluoroquinolones and amikacin only when resistance is suspected despite the absence of previously identified genetic mutations associated with DR to these medicines, as commercially available rapid genetic methods such as the second-line line-probe assays detect

approximately 85% of fluoroquinolones- or two thirds of aminoglycoside resistance mutations.

## Determining critical concentrations for DST

DST results should be able to clearly differentiate between susceptible and resistant, and should help physicians prescribe effective anti-TB therapy. DST for second-line anti-TB agents should be built on the foundation of reliable, quality-assured first-line DST. In 2018, critical concentrations were revised or established for performing DST for the WHO Group A drugs that are strongly recommended in the treatment of DR-TB. These include the later-generation fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline, and linezolid. A critical concentration for the oral core agent clofazimine was established for MGIT medium only. Critical concentrations for the Group C (add on) agents were established or validated for delamanid, amikacin, and pyrazinamide. Knowledge of pyrazinamide susceptibility can inform decisions on the choice and design of effective DR-TB regimens. Culture-based pyrazinamide phenotypic DST is difficult to perform and can produce unreliable results. Currently, BACTEC MGIT 960 liquid culture method is the only WHO-recommended method for pyrazinamide DST, even though a high rate of false-positive resistance results has been reported in some laboratories. In a quality-assured laboratory, pyrazinamide DST in MGIT can be performed reliably and reproducibly. The lack of WHO-recommended molecular test to diagnose pyrazinamide resistance ahead of treatment start implies that even where pyrazinamide DST is available, the results usually only become accessible after treatment has been initiated. The detection of resistance-conferring mutations in the pncA gene using DNA sequencing is the most reliable method for rapid detection of pyrazinamide resistance although there is emerging evidence of mutations other than pncA conferring pyrazinamide-resistance.

Treatment for MDR-TB is increasingly becoming more individualised as a result of innovations in diagnostics and growing scientific understanding of the molecular basis for DR and the pharmacokinetics and pharmacodynamics of TB medicines. Availability of new NGS-based tests able to detect mutations associated to DR on multiple targets makes it possible to predict resistance to first- and second-line drugs from smear positive clinical samples. Two signals are clear from the current scientific evidence assessment: (a) the feasibility of effective and full-oral treatment regimens for most patients; (b) the need to ensure that pre-XDR and XDR are excluded (at least to the fluoroquinolones and amikacin) before starting patients on treatment, especially for the shorter MDR-TB regimen. When countries switch to all-oral regimens, the need to exclude resistance to amikacin will be less useful.

DST should be performed at the time of treatment initiation (Figure 2) against the drugs for which a reliable method is available. If baseline DST is not possible, DST should be performed on the first positive culture isolated from the patient during treatment monitoring. Positive cultures isolated from patients during treatment monitoring should be stored frozen in glycerol. If DR or treatment failure is suspected, phenotypic DST and NGS, if available, should be performed to collect data on mutations that may be associated with TB DR, especially for the newer drugs.

In response to this challenge, high-TB burden countries must upgrade and streamline their laboratory networks. Molecular techniques should replace phenotypic methods for initial diagnosis and detection of DR, while traditional cultures will still be needed during follow-up to detect viable bacilli. At least at central level capacity to perform DST for bedaquiline, linezolid, clofazimine and delamanid should be established. The Xpert system should be introduced at point-of-care facilities for rapid detection of RR, and Line Probe Assays (LPAs) can diagnose MDR-TB and XDR-TB in just a couple of days, allowing for the early institution of effective treatment.

## How to design the regimen

A patient-tailored clinical strategy focused on good adherence is necessary to achieve high treatment success rates for MDR-TB patients (Figures 1 and 2,Table 1). In particular, the need to individualize treatment regimens has been recently emphasized,

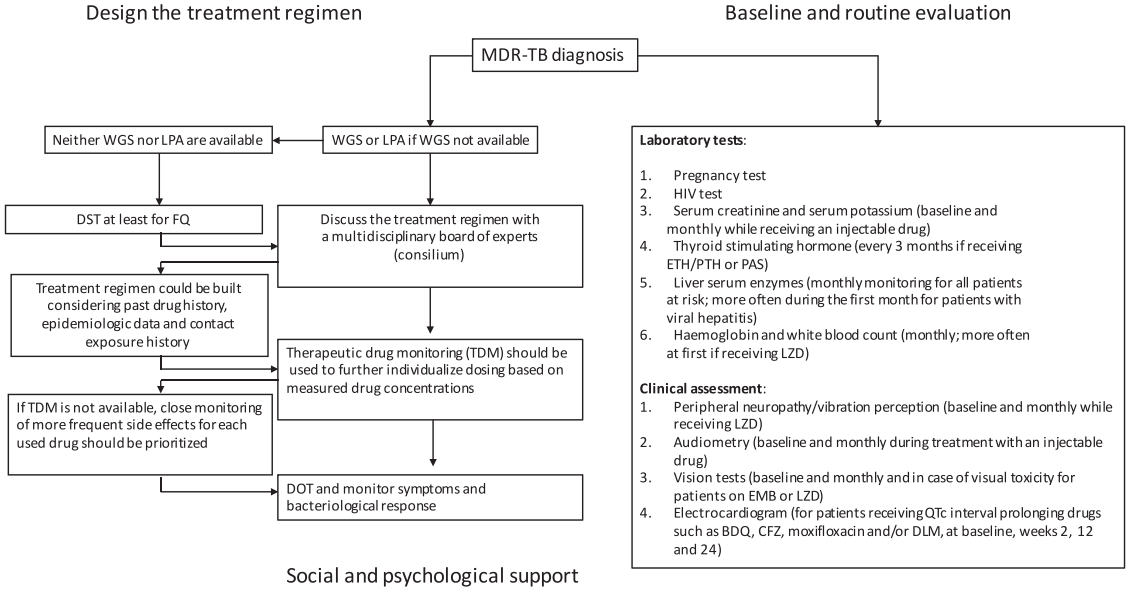


**Figure 2.** Clinical management of patients with multidrug-resistant tuberculosis.
MDR-TB: multidrug-resistant tuberculosis; WGS: whole genome sequencing; LPA: line probe assay; DST: drug-susceptibility testing; DOT: directly observed therapy; ETH/PTH: ethionamide/prothionamide; PAS: para-aminosalicylic acid; LZD: linezolid; QTc interval: corrected measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; BDQ bedaquiline; CFZ: clofazimine; DLM: delamanid.

taking into account the DR pattern of the putative *M. tuberculosis* strain.

Treatment success depends on the ability of the treating team to monitor and manage adverse events and concomitant comorbidities (e.g., HIV-infection, diabetes mellitus, alcoholism, etc.), potential drug-drug interactions, patient's preferences and tolerability (e.g., administration of second-line injectable drugs) in addition to designing an effective treatment regimen (Akkerman et al., 2019; Borisov et al., 2019; Nahid et al., 2019; World Health Organization, 2019b). In individuals with pauci-bacillary disease (e.g., children, HIV co-infected individuals) and without the confirmation of a specific DST pattern, the regimen should be tailored to the DST findings of the potential index case or the MDR-TB epidemiology of the geographical area where the patient resides (Nahid et al., 2019).

However, as designing the regimen and managing the MDR-TB patient is difficult, a multi-disciplinary approach is recommended, assisted by a MDR-TB Consilium, MDR-TB cohort or equivalent expert support. In addition to regional and national TB Consilia, a supranational cost-free and multilingual platform is available offering validated and vetted advice in clinical management, within 48 h (Global TB Consilium: http://www.waidid.org/site/workinggroups). According to the ATS/CDC/ERS/IDSA guidelines the regimen should include five drugs during the intensive phase and four drugs during the continuation phase (Nahid et al., 2019), with a treatment duration between 15 and 21 months after culture conversion for MDR-TB and between 14 to 24 months for pre-XDR/XDR-TB patients (Nahid et al., 2019). The intensive phase (aimed at significantly decreasing the bacillary burden) should range from 5 to 7 months (Nahid et al., 2019) after culture conversion according to the same document.

According to the consolidated WHO MDR-TB guidelines (World Health Organization, 2019b), 4 oral drugs are recommended in the intensive phase and at least 3 in the continuation phase of treatment, with a total treatment duration of 18–20 months for most patients. In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients, with an intensive phase of 6–7 months when the longer regimen includes amikacin or streptomycin: the treatment durations mentioned above may be modified according to the patient's response to therapy (World Health Organization, 2019b).

Six consecutive steps are recommended (Figure 1) by the recent ATS/CDC/ERS/IDSA guidelines, published in 2019. Step one implies the prescription of one later-generation fluoroquinolone (i.e., levofloxacin, moxifloxacin), followed by (Step 2) two high-priority drugs (i.e., bedaquiline and linezolid). Step 3 includes two other highly effective drugs (i.e., clofazimine, cycloserine). The need for Step 4 depends on the strain's susceptibility pattern: in case of DR to one or more of the above-mentioned drugs and the impossibility to have 5 active drugs we need to choose one injectable drug (amikacin or streptomycin). If needed or a full oral regimen is preferred, injectables should be replaced by delamanid, pyrazinamide, or ethambutol (Step 5: the last two medicines only if confirmed susceptibility to these agents). A complicated DR pattern preventing the prescription of a 5-drug regimen based on the above-mentioned medicines implies the need for different agents (Step 6). The ATS/CDC/ERS/IDSA guidelines assign lower priority to the administration of ethionamide/prothionamide, imipenem/meropenem plus clavulanate, para-aminosalycilic acid, high-dose isoniazid, based on their poor effectiveness to decrease mortality or inability to increase the treatment success rate, or route of administration (Nahid et al., 2019). Capreomycin, kanamycin, macrolides, and amoxicillin/clavulanic acid (the latter should only be administered with a carbapenem-containing regimen) are no longer recommended (strong recommendation).

With regard to injectables, they require more time to prepare, administer, and monitor; consume patient and staff time; are less liked by patients; and invariably raise costs. Amikacin is an effective drug against DR tuberculosis as demonstrated in previous IPD metanalyses. However, it has been replaced by more effective, oral and less toxic medications; this does not mean that it cannot be useful in settings where it can be administered and monitored safely. Recently published and unpublished experiences suggest carbapenems are effective in patients with complex resistance profiles (Arbex et al., 2016; The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment-2017 et al., 2018; Tiberi et al., 2016a, 2016b).

## Clinical management

As the clinical management of MDR-TB patients is complicated (Figure 2), an adequately planned management model balancing available specialized resources and prevalence of disease is required. Thus, in countries with low prevalence and high resources (e.g. Western European countries, North America) it should ideally be carried out in MDR-TB reference centres, where skilled clinicians can operate in the presence of adequate infrastructure and pathways (infection control, palliative care, quality-controlled laboratory, access to cohort and consilium advice) (Migliori et al., 2019). Conversely, in settings with limited resources and high prevalence of MDR-TB a decentralized model of care has proven to be effective, and is advisable (Loveday et al., 2018). In this latter case, only complicated cases are referred to specialized centres or proposed to local/international TB consilia.

Details on the use of molecular testing and DST as well as on the principles to design an effective regimen treatment duration are provided in Figures 1 and 2 and in the previous sections (Nahid et al., 2019; World Health Organization, 2019b).

Treatment design should be based only on proven or highly probable drug susceptibility, 'in-vitro' or based on clinical and epidemiological information (e.g., the DR pattern of the index patient, or the most updated epidemiological data on the prevalent drug resistances in a specific setting).

Given the relative difficulty and cost of sampling patients on a weekly basis and the lack of approved biomarkers, duration of treatment continues to be an amalgamation of clinical and radiological data, a lack of positive microbiology, and erring on the side of caution.

More research is necessary to give a final verdict on the efficacy/effectiveness of standardized shorter-course regimens lasting $\leq$12 months in comparison with effective longer all-oral regimens (Nahid et al., 2019). It is possible that the use of new drugs, particularly in some forms of pauci-bacillary or extrapulmonary TB might require, in the future, shorter regimens than more severe cavitary forms; however, more data is needed to dictate shorter durations of treatment.

WHO recommends the use of shorter 9–12 month regimens (4–6 months with amikacin-moxifloxacin-ethionamide[prothionamide]-clofazimine-pyrazinamide-high dose isoniazid/ethambutol/5 months with moxifloxacin-clofazimine-pyrazinamide-ethambutol) when the DR pattern is not complicated based on the findings of the STREAM trial (Nunn et al., 2019). This should be used only for the regimens including injectables, but after a recent literature review, WHO has updated recommendations and is now phasing out the shorter injectable-containing regimens and recommending a shorter all-oral bedaquiline-containing regimen for eligible MDR/RR-TB patients under specific conditions (World Health Organization, 2019e). However, due to the long half-life of bedaquiline, patients started on an all-oral regimen lost to follow-up may be exposed to potential bedaquiline monotherapy, with a potential risk of developing DR. Recent evidence suggests that

adequate management of injectables in specific patients minimizes adverse events (Borisov et al., 2017; Piubello et al., 2020).

Following the results of the NIX TB trial (World Health Organization, 2019e) and the US FDA (Food and Drug Administration) approval in patients with XDR-TB, a shorter regimen with bedaquiline, pretomanid and linezolid (BPaL regimen) may be used (under operational research conditions and no previous use of bedaquiline and linezolid) as an alternative to the longer regimen. If pretomanid-containing regimens are used under operational conditions, capacity to test for the drug should be equally considered.

In selected patients with strong risk of relapse and treatment failure (and localised pulmonary sequelae), elective partial lung resection (e.g., lobectomy or wedge resection) has been recommended in addition to an adequately designed MDR-TB regimen (Nahid et al., 2019).

During follow-up close monitoring of the treatment response is recommended: patients should be assessed clinically (symptoms and clinical signs recovering, including weight gain for children), radiologically, and bacteriologically (culture positivity evaluated monthly). In the case of culture remaining positive after three months of treatment, phenotypic DST should be repeated to detect if new DR has occurred (Nahid et al., 2019). When drug-susceptible DST does not match with the patients' clinical progress, underlying DR or malabsorption can be responsible, and further investigations like therapeutic drug monitoring (TDM) might be necessary.

During follow-up visits, patients should thoroughly be questioned about the occurrence of drug-related adverse events: they could decrease patient's adherence, increasing the probability of new DR. Adverse events should be notified to the national programme, ideally within a comprehensive aDSM (active drug-safety monitoring and management) system (Akkerman et al., 2019; Borisov et al., 2019).

TDM is helpful to detect low drug exposure in case of lack of response or drug-related adverse events (Nahid et al., 2019). Based on the measured drug concentration, drug dosages can be adapted to optimize the treatment. Proactive use of TDM can help to prevent drug-related complications in patients with risk factors for either low or high drug exposure (Nahid et al., 2019; World Health Organization, 2019b). TDM has been recommended for patients with gastrointestinal problems (e.g. affecting absorption of the drug), renal or hepatic problems (e.g. low clearance of the drug), comorbidities like diabetes type2 and HIV or drug-drug interactions (Nahid et al., 2019). For the maximum benefit, samples for TDM need to be collected at the right time and in the right manner, analyzed in a timely fashion and correctly interpreted, resulting in a dose adjustment recommendation to the clinician (Alffenaar et al., 2019). Clearly, a good understanding of bioanalytical procedures and clinical pharmacologically is required to develop a TDM for a programmatic setting (Alffenaar et al., 2019). The use of different sampling strategies like saliva and dried blood spot in addition to plasma or serum will allow a simple semi-quantitative screening to detect low drug exposure as well as precise TDM in those with detected low exposure (Alffenaar et al., 2019b, 2019a).

A patient-centered approach is recommended after the diagnosis of MDR-TB, as suggested by the WHO End TB Strategy in its first pillar (World Health Organization, 2015a; World Health Organization, 2019d). Clinicians should clearly explain the risks associated with the disease (e.g., transmission of *M. tuberculosis* strains in case of inappropriate therapy), and with the therapy (e.g., potential occurrence of adverse events, importance of adherence to treatment). Patients should be actively involved in the choice of the drug regimen (use of injectable-containing versus full-oral regimen), and in the management of concomitant comorbidities and potential drug-drug interactions (Nahid et al., 2019; World Health Organization, 2019b).

The time-span of isolation of MDR/XDR patients is often a matter of debate in TB consilia, and unequivocal guidelines for de-isolation of patients in general are missing (Petersen et al., 2017). WHO and CDC guidelines may be interpreted as requiring MDR-TB patients to be isolated as long as they are culture-positive, but the recent consensus document from WHO Europe has reviewed the literature extensively and has shown the importance of effective treatment for duration of isolation (Migliori et al., 2019). Sputum may be culture-positive for 1-2 months after treatment initiation (Fitzwater et al., 2010) and afterwards there is a 2-month delay for the culture result to come out as negative, unless liquid cultures are in use, implying 3-4 months of isolation, perhaps hospitalization. Yet, also some MDR-TB patients are no longer infectious after 2 weeks of effective treatment (Dharmadhikari et al., 2014), although special caution should be taken in case of highly smear-positive cases – as in cavernous disease (Dharmadhikari et al., 2014; Imperial et al., 2018; Menzies, 1997; Petersen et al., 2017; Migliori et al., 2019). These patients remaining infectious as long as they are sputum smear or culture positive seems to be unfounded, and although MDR-TB patients remain culture-positive longer (Telzak et al., 1997), this is a result of being on ineffective treatment initially. Once an effective treatment has been established, MDR-TB patients are also likely to reduce infectiousness rapidly. Therefore, 3–4 months of isolation is not warranted (Petersen et al., 2017; Rouillon et al., 1976) while isolation beyond 2 weeks of treatment is warranted because of the risk of non-effective treatment since full susceptibility results may not be available at the time of treatment initiation. New RNA-based molecular tests may in the future be used to monitor infectiousness and response to treatment without the delay linked to the use of culture.

## Management of children with MDR-TB

Given the difficulty of microbiological confirmation in children, MDR-TB is often a presumptive diagnosis, although microbiological confirmation should always be pursued. Use of the new Xpert Ultra is advised in children given increased sensitivity in patients with pauci-bacillary disease. (Zar and Nicol, 2019). Children diagnosed on clinical grounds, following recent (in the past 12 months) close contact with an infectious MDR-TB source case, should be treated according to the DST results of the likely source case. The principles of treatment are similar to those articulated for adults, but the rationale for using injectable-free regimens is even stronger given the devastating consequences of hearing loss in early life (Seddon et al., 2018). Although the same drugs used in adults are used in older children, bedaquiline is currently not advised in children less than 6 years of age (<15 kg) given the absence of pharmacokinetic and safety data (The Sentinel Project for Pediatric Drug-Resistant Tuberculosis, 2018). Bedaquiline may be replaced by delamanid in children 3-6 years of age, but cannot be given to children <3 years of age (<10 kg) for the same reason (Huynh and Marais, 2019; World Health Organization, 2016). In young children (<3yrs of age) alternative second-line drugs should be considered (Schaaf et al., 2018). Children with pauci-bacillary disease may sometimes be treated for a shorter duration (19–15 months) if an adequate regimen is given, and the treatment response is good and is well tolerated. Child-friendly drug formulations should be used whenever possible, and all relevant co-morbidities, such as HIV co-infection and malnutrition, considered and addressed. In children with MDR-TB meningitis, careful consideration should be given to central nervous system and cerebrospinal fluid penetration of the various drugs (Huynh et al., 2019). With optimal management, excellent outcomes have been reported in children with MDR and even XDR-TB (Harausz et al., 2018).

**Table 2**
Evidence of treatment of latent tuberculosis infection in contacts of multidrug-resistant tuberculosis.

| Study/trial | Study population/Aim | Design/treatment | Adverse events and outcome | Reference |
|---|---|---|---|---|
| TrialTB-CHAMP | Household MDR TB contacts; only children < 5 years old – South Africa (enrolling)<br>Aim: To evaluate the efficacy of levofloxacin vs. placebo for prevention of MDR-TB in young children following household exposure | Multi-centre, randomized double blind placebo-controlled trial<br>6 months of parent-administered oral levofloxacin once per day, vs 6 months of placebo in the control group; followed for 18 months after treatment completion | Not reported | WHO International Clinical Trials Registry Platform, identifier: ISRCTN92634082 |
| TrialPHOENIx MDR-TB | Household MDR TB contacts; all ages – multiple countries (enrolling)<br>Aim: To evaluate the protective effect delaminid vs. isoniazid for prevention of M/XDR-TB following household exposure | Unblinded, randomized comparative trial<br>Compare efficacy and safety of 26 weeks of delamanid versus 26 weeks of isoniazid for preventing confirmed or probable active TB during 96 weeks of follow-up among high-risk household contacts of M/XDR-TB adults | Not reported | ClinicalTrials.gov identifier: NCT03568383 |
| V-QUIN MDR TRIAL | Household MDR TB contacts; all ages – Vietnam (completed enrolling)<br>Aim: To evaluate the efficacy of levofloxacin vs. placebo for prevention of MDR-TB following household exposure | Double-blind parallel group RCT<br>6 months of self-administered oral levofloxacin once per day, vs 6 months of placebo in the control group; followed for at least 24 months after treatment completion | Not reported | <**Australian New Zealand Clinical Trials Registry (ANZCTR), identifier: ACTRN12616000215426 |
| Meta-analysis | Meta-analysis of treatment of LTBI using PICO questions following Cochrane procedures<br>To assess whether treatment of LTBI from MDR-TB contacts is significantly associated with lower tuberculosis incidence, compared with no medical treatment | The most effective regimen included a fluoroquinolone combined with ethionamide<br>The most cost-effective regimen included fluoroquinolone/ethambutol, followed by fluoroquinolone alone, then by pyrazinamide/ethambutol | Pyrazinamide regimens reported up to 66% adverse events<br>The regimen was considered cost-effective. | Marks et al. (2017) |
| Case series of close MDR-TB contacts | Prevent development of clinical MDR-TB | Fifty contacts of HIV- and MDR-TB patients treated with moxifloxacin; 30 patients completed the regimen in New York City | Three discontinued treatment because of gastrointestinal symptoms. | Trieu et al. (2015) |
| Case series of close MDR-TB contacts | Twelve consecutive contacts to an MDR TB case<br>The aim of the study was to describe the adverse events related to combined pyrazinamide and ethambutol to treat LTBI | Observational case series, The regimens consisted of pyrazinamide ($23 \pm 4$ mg per Kg BW) and ethambutol ($17 \pm 4$ mg per Kg BW) | Treatment was discontinued in seven cases (58%) after a median of 119 days, due to hepatotoxicity in six cases (ALT or AST elevation more than four times the upper normal limit), and gastrointestinal symptoms in one case | Younossian et al. (2005) |
| Open label, comparative study | 186 children were included as contacts of 164 MDR-TB source patients<br>They underwent 12 months follow-up in South Africa | Ofloxacin (15–20 mg/kg BW daily plus ethambutol (20–25 mg/kg BW daily), or isoniazid (15–20 mg/kg BW daily) for 6 months | 7 (3.7%) children developed grade 3 adverse events<br>One child died and 6 developed active TB (of whom 5 had poor adherence) | Seddon et al. (2013) |
| Case series of close MDR-TB contacts | 119 contacts of MDR-TB patients were followed-up in Micronesia<br>Of the 104 who initiated treatment, 93 (89%) completed the regimen | None receiving treatment developed active TB.3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB<br>When *M. tuberculosis* strains were resistant to isoniazid, rifampicin and ethambutol the regimens were as follows: Adults aged >12 years received oral moxifloxacin 400 mg daily and ethambutol 15 mg/Kg BW daily for 12 months Children aged ≤12 years received oral levofloxacin 20 mg/Kg BW daily and ethambutol 15 mg/Kg BW daily for 12 months When *M. tuberculosis* strains were resistant to isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin the regimen included:<br>Adults aged >12 years: oral moxifloxacin 400 mg daily for 12 months;<br>Children aged ≤12 years: oral levofloxacin 20 mg/kg BW daily and oral ethambutol 20 mg/kg BW daily for 12 months | 4 contacts discontinued due to adverse events | Bamrah et al. (2014) |
| Case series close MDR-TB contacts | Prevent development of TB after exposure to an MDR-TB index patient | 31 children with LTBI after exposure, 26 treated with levofloxacin and pyrazinamide | 12 children required treatment changes because of adverse events. | Adler-Shohet et al. (2014) |
| Case series (retrospective audit of paediatric management) | The audit identified between 2006 and 2010 23 children in 6 centres of England who were contacts of confirmed MDR-TB index cases | Of 23 children, 8 were non-infected and 12 with confirmed LTBI, 8 (66.7%) were treated with 2 drugs for a median of 6 months (range 6-12 months) based of the drug-susceptibility pattern of the index case. No details of the regimes are provided | All 12 children (including the 10 who completed the 24 month follow-up) were well and did not report adverse events or TB | Williams et al. (2013) |
| Case series | Occupational exposure to MDR TB resistant to rifampicin, isoniazid, streptomycin, and ethambutol in New York City | Sixteen health care workers entered a six-month investigational trial of ofloxacin (800 mg a day) and pyrazinamide (1500 mg a day) | 14 cases discontinued LTBI treatment after less than 6 months; 13 reported one or more adverse events, including arthralgia (7), gastrointestinal distress (6) and hepatitis | Horn et al. (1994) |

**Table 2** (*Continued*)

| Study/trial | Study population/Aim | Design/treatment | Adverse events and outcome | Reference |
|---|---|---|---|---|
| Case series | Seventeen individuals with presumed LTBI MDR-TB infection | Treated with pyrazinamide and levofloxacin | Fourteen individuals developed musculoskeletal adverse events (11 probably related to combination therapy) and 8 central nervous ones Hyperuricemia, gastrointestinal and dermatological effects were also common.Therapy was discontinued in all of them | Papastavros et al. (2002) |

MDR-TB: multidrug-resistant tuberculosis; LTBI: latent tuberculosis infection; PICO: population, intervention, comparison, and outcome; ALT-AST: alanine amino transferase and aspartate amino transferase; BW: body weight.

## Contact investigation and treatment of latent TB infection in MDR-TB contacts

While rates of DR-TB are proportionately higher in persons previously treated for TB, the burden of MDR-TB is larger in persons who have never been treated for TB, a consequence of transmission of DR bacilli in the community. Thus, 54% of MDR-TB occurs among patients who had never received TB treatment (Kendall et al., 2015). In one study 7.8% of household contacts of MDR-TB patients developed TB, mostly occurring within one year of index case's diagnosis (Shah et al., 2014). Until recently, there was no consensus to provide preventive treatment to contacts of infectious MDR-TB patients, but this has changed in the new ATS/CDC/ERS/IDSA Clinical Practice Guideline (Nahid et al., 2019). A systematic review on 21 relevant papers found that the estimated MDR-TB incidence reduction was 90% with preventive treatment (Marks et al., 2017). Hence, preventive treatment of MDR-TB contacts with LTBI is currently recommended based on the above observation.

Several randomised clinical trials are currently ongoing to determine a single-drug preventive treatment regimen for MDR-TB contacts; these are the PHOENIx trial (delamanid versus isoniazid) and the V-QUIN and TB- CHAMP clinical trials (levofloxacin versus placebo in adults and children, respectively). While results of these trials are awaited, preventive treatment should be determined on the basis of the DST results of the source-case's *M. tuberculosis* isolate.

If possible, a later-generation fluoroquinolone alone or with a second drug such as ethambutol should be used (Nahid et al., 2019). Pyrazinamide should not be used as the second drug, because of higher adverse events and discontinuations. The evidence available is summarised in Table 2. (Adler-Shohet et al., 2014; Bamrah et al., 2014; Horn et al., 1994; Marks et al., 2017; Papastavros et al., 2002; Seddon et al., 2013; Trieu et al., 2015; Williams et al., 2013; Younossian et al., 2005).

## Functional evaluation and rehabilitation post-TB

Recent evidence shows that about half of pulmonary TB patients completing treatment suffer from the consequences of sequelae with obstructive, restrictive and mixed functional patterns (Muñoz-Torrico et al., 2016; Tiberi et al., 2019).

The extent of pulmonary sequelae is likely to be associated with initial bacterial burden, extent of inflammation and the accompanying duration of treatment, being more important among MDR-/XDR-TB patients (especially if they had prior episodes of TB) than among drug-susceptible ones (Muñoz-Torrico et al., 2016; Tiberi et al., 2019).

A complete post-TB treatment functional evaluation has been recommended including radiology, spirometry with bronchodilator response, assessment of lung volumes (plethysmography), carbon monoxide diffusion capacity of the lung (DLCO), arterial blood gases analysis; 6-min walking test (6MWt) and quality of life evaluation (Muñoz-Torrico et al., 2016; Tiberi et al., 2019).

Pulmonary rehabilitation proved to be effective in improving the above-mentioned parameters (Spruit et al., 2013; Visca et al., 2019). Further research is necessary to identify setting-specific models and programmatic feasibility of these interventions (Muñoz-Torrico et al., 2016; Spruit et al., 2013; Tiberi et al., 2019; Visca et al., 2019).

## Public health management

The principles of public health management are centered around achieving high success rates when treating drug-susceptible cases and trying to diagnose and cure the highest possible proportion of cases with MDR-TB while preventing further transmission within the community (Pontali et al., 2013).

The importance of administrative and environmental control measures as well as of personal protection (masks for infectious patients and respirators to protect health care workers and visitors from potential infections) has been recently emphasised (Migliori et al., 2019; Migliori et al., 2018; World Health Organization, 2019). WHO strongly advocates for a reduction of unnecessary admissions of MDR-/XDR-TB cases which need to be limited to severe cases with life-threatening conditions, adverse events and co-morbidities, while reducing as much as possible admission for 'social reasons' (Migliori et al., 2019; Migliori et al., 2018; World Health Organization, 2019). Recent WHO European guidance provides criteria for units admitting infectious cases, including the availability and necessary standards of infection control measures, quality-controlled laboratory services, adequately trained staff and palliative care service, among others (Migliori et al., 2019; Migliori et al., 2018; World Health Organization, 2019).

From a programmatic perspective all the necessary components required to diagnose and treat MDR-TB should work adequately within a coherent National Strategic Plan (World Health Organization, 2015b): quality-controlled laboratory network; drug procurement; clinical services; surveillance, and monitoring and evaluation.

## Conclusions

Although a significant advance in diagnosis and treatment has been achieved with the existing (and new) rapid molecular diagnostics, as well as with the BPaL shortened regimen, further research investments are necessary on fast patient triage and all-oral shorter and better tolerated regimens. On top of further improving the existing diagnostic, treatment and prevention tools, universal access and correct programmatic use are needed in all settings, in order to implement the three pillars of the End TB strategy (1. Integrated, patient-centred care and prevention; 2. Bold policies and support systems; 3. Intensified research and innovation) and meet its goal and targets.

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No competing interest declared.

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## Appendix A.

The Global Tuberculosis Network (GTN) Collaborators who contributed to this article are:

T. Abu Arkub (Russian Federation); O.W. Akkerman (Netherlands); A. Aleksa (Belarus); E. Belilovski (Russian Federation); E. Bernal (Spain); F-X. Blanc (France); M. Boeree (Netherlands); S. Borisov (Russian Federation); J. Bruchfeld (Sweden); J. Cadiñanos Loidi (Spain); J.A. Caminero (Spain); A.C. Carvalho (Brazil); J. J. Cebrian Gallardo (Spain); M. Charalampos (Greece); E.Danila (Lithuania); L.Davies Forsman (Sweden); J. Denholm (Australia); K. Dheda (S.Africa); R.Diel (Germany); S. Diktanas (Lithuania); C. Dobler (Australia); M. Enwerem (S.Africa); S. Esposito (Italy); N. Escobar Salinas (Chile); A. Filippov (Russian Federation); B. Formenti (Italy); J.M, García García (Spain); D. Goletti (Italy); R. Gomez Rosso (Paraguay); G. Gualano (Italy); P. Isaakidis (S.Africa); A. Kaluzhenina (Russian Federation); S. Koirala (Nepal); L. Kuksa (Latvia); H. Kunst (UK); Y. Li (China); C. Magis-Escurra (Netherlands); V. Manfrin (Italy); S. Manga (Peru); K. Manika (Greece); V. Marchese (Italy); E. Martínez Robles (Spain); A. Maryandyshev (Russian Federation); A. Matteelli (Italy); A. Mariani (Brazil); J. Mazza-Stalder (Switzerland); F. Mello (Brazil); L. Mendoza (Chile); A. Mesi (Albania); S. Miliauskas (Lithuania); H. Mustafa Hamdan (Sudan); N. Ndjeka (S.Africa); M.Nieto Marcos (Spain); T.H.M.Ottenhoff (Netherlands); D.J.Palmero (Argentina); F. Palmieri (Italy); A. Papavasileiou (Greece); M.C Payen (Belgium); A. Pontarelli (Italy); M.Pretti Dalcolmo (Brazil); S. Quirós Fernandez (Spain); R. Romero (S.Africa); D. Rossato Silva (Brazil); A.P. Santos (Brazil); B. Seaworth (USA); M. Sinitsyn (Russian Federation); A. Skrahina (Belarus); I. Solovic (Slovakia); A. Spanevello (Italy); M. Tadolini (Italy); C.Torres (Colombia); Z. Udwadia (India); M. van den Boom (Denmark); G.V. Volchenkov (Russian Federation); A. Yedilbayev (Denmark); R. Zaleskis (Latvia); J.P. Zellweger (Switzerland).

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